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DEPARTMENT OF ANESTHESIOLOGY

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January 10, 1973

Drs. Sheldon C. Sommers and Robert C. Hockett
The Council for Tobacco Research-U.S.A., Inc.
110 East 59th Street
New York, New York 10022

Dear Drs. Sommers and Hockett:

I thank you for the interview which you granted me on January 4, 1973 in connection with the proposed extension of Grant number 725.

Following preliminary research work done in the last six months and after discussing the matter with you, I feel the following relevant points should be made with regards to the course of study to be followed in connection with the project entitled "Changes in tracheobronchial cytology;" and based on the following points:

1) During the period: October 1, 1969 to July 1, 1972 smears from 1,365 anesthetized women were analyzed in relation to nuclear position changes and goblet cell percentage variations during the menstrual cycle and the effect of old age, pregnancy and exogenously administered sex hormones on these cytologic changes.(1)

"Cyclic cytomorphologic and cytochemical changes were noted in the epithelia of younger women but not in the epithelia of older women and males. During the proliferative phase of the menstrual cycle the nuclei of the ciliated cells were found mainly in the basal position. Following ovulation they ascended to mid-position, and as the secretory phase progressed they migrated towards the apex. After approximately the 25th day, increasing numbers of cells with basal nuclei were again noticed. Intracytoplasmic mucopolysaccharide content increased with the ascent of the nucleus. When cells with basal nuclei predominated once more, goblet cells proliferated concurrently, probably indicating metaplsia from ciliated cells with high mucopolysaccharide content."

It was assumed that these cyclic fluctuations might probably protect females from inhaled irritants and carcinogens.

2) In order to assess the effects of cigarette smoking on the cyclic variations described above, efforts were made to compare nuclear position variations and goblet cell percentage changes between women with different smoking habits. It was found that there were very little

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differences in that respect between non smokers and light and medium smokers. Heavy smokers, however, displayed generally increased goblet cell percentages and a less marked nuclear position variation during the menstrual cycle.

3) Damage to the components of the ciliated epithelial cells (cilia, end plate, nucleus and cytoplasm) was noted in several smears and appeared at first to be more marked in patients who had breathed dry anesthetic gases.(2) A special study was conducted on healthy non smokers of both sexes using a point scoring system to assess damage numerically and it was found that dry gases produced significant cytologic damage if used for over an hour whereas gases with a 60% humidity at room temperature and fully humidified at body temperature did not, for periods in excess of three hours.

4) Cellular damage caused by dry anesthetic gases are not specific and similar changes are found between the various smoking groups. This is in accordance with histologic studies made by Auerbach et al (3) who also describe increases in goblet cell percentages in smokers.

Based on the last two points, a pilot study was conducted on a group of 180 patients to try and correlate smoking habit with preoperative lung function tests, percentages of normal cytologic features at the onset of anesthesia and postoperative complication rate. In addition a special study subgroup was formed in which smoking habit was correlated with rate of decay of cytologic features between the onset and end of anesthesia when dry and humidified gases were used.

Preoperative lung function tests (figure 1) differed little between non smokers, light, medium and heavy smokers but there was a marked decrease in lung function in very heavy smokers. These results are similar to those obtained by other authors (4-6). The correlation between preoperative lung function and postoperative complication rate was of the order of R = 0.65.

The percentage of normal cytologic features at the onset of anesthesia, on the other hand, varied markedly between the various smoking groups being highest in non smokers and lowest in very heavy smokers (figure 2). In this instance the correlation coefficient between intraoperative cytology (at the onset of anesthesia) and therate of postoperative complications was 0.92, thus indicating a much closer relationship between these two factors.

The rate of cytologic decay during anesthesia (table 1) did not vary between light and non smokers and medium and heavy smokers if the gases were humidified, whereas when dry gases were used, light and non smokers fared best.

Considering the results obtained thus far, it is felt that a two year special study should be conducted to try and correlate the possible

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protective effects of female hormones with cytologic damage caused by smoking, preoperative lung function and postoperative complication rate.

In fact, if damage to the cells caused by smoking was found to vary with alterations in goblet cell percentage in younger women during the menstrual cycle and if this could be correlated with a decreased postoperative complication rate and improved lung function, our assumption that females are indeed protected by their sex hormones against bronchogenic carcinoma (and possibly obstructive lung disease) would be strengthened.

The following line of study is proposed:

1) To study a group of young female patients subdivided by smoking habit (amount and duration); all patients being about to undergo routine surgery under general endotracheal anesthesia.

Investigation to include:

a) Relevant history and required historical data
b) Preoperative lung function tests (Peak expiratory flow rate, FEV1 and FEV3)
c) Study of tracheobronchia smears obtained at the onset of anesthesia in relation to:

   i) Nuclear position
   ii) Percentage of goblet cells
   iii) Calculation of the percentage of normal cellular features

d) Postoperative evaluation including the monitoring of temperature, examination of the chest (physically and Roentgenologically if needed) and blood gas analysis if relevant.

2) Controls to include older females and males of various age groups and of various smoking habits.

3) A special study on the possible protective effects of exogenous hormones and other steroids in patients receiving these drugs preoperatively or intraoperatively for therapeutical reasons.

4) A study to evaluate the resistance to dry anesthetic gases between various smoking groups of both sexes (cytology and postoperative follow up).

5) To continue the search for mallignant cells appearing from time to time in smears and to arrange for the follow up of patients producing these cells.

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In addition as there seems to be a racial and environmental influence on the incidence of bronchogenic carcinoma (7) it may be advisable to repeat the original hormone study in Japan. Arrangements have already been made to put this into action should the Council feel that it would be of interest.

Sincerely yours,

J. Chalon, M.D.
Assistant Professor

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APPENDIX 1

ABBREVIATIONS USED IN FIGURES 1 AND 2

Smoking Groups:
0 Non smoker
1 Light smoker (1-9 cigarettes a day)
2 Medium smoker (10-19 cigarettes a day)
3 Heavy smoker (20-29 cigarettes a day)
4 Very heavy smoker (over 30 cigarettes a day)

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Source: https://www.industrydocuments.ucsf.edu/docs/jyal0000

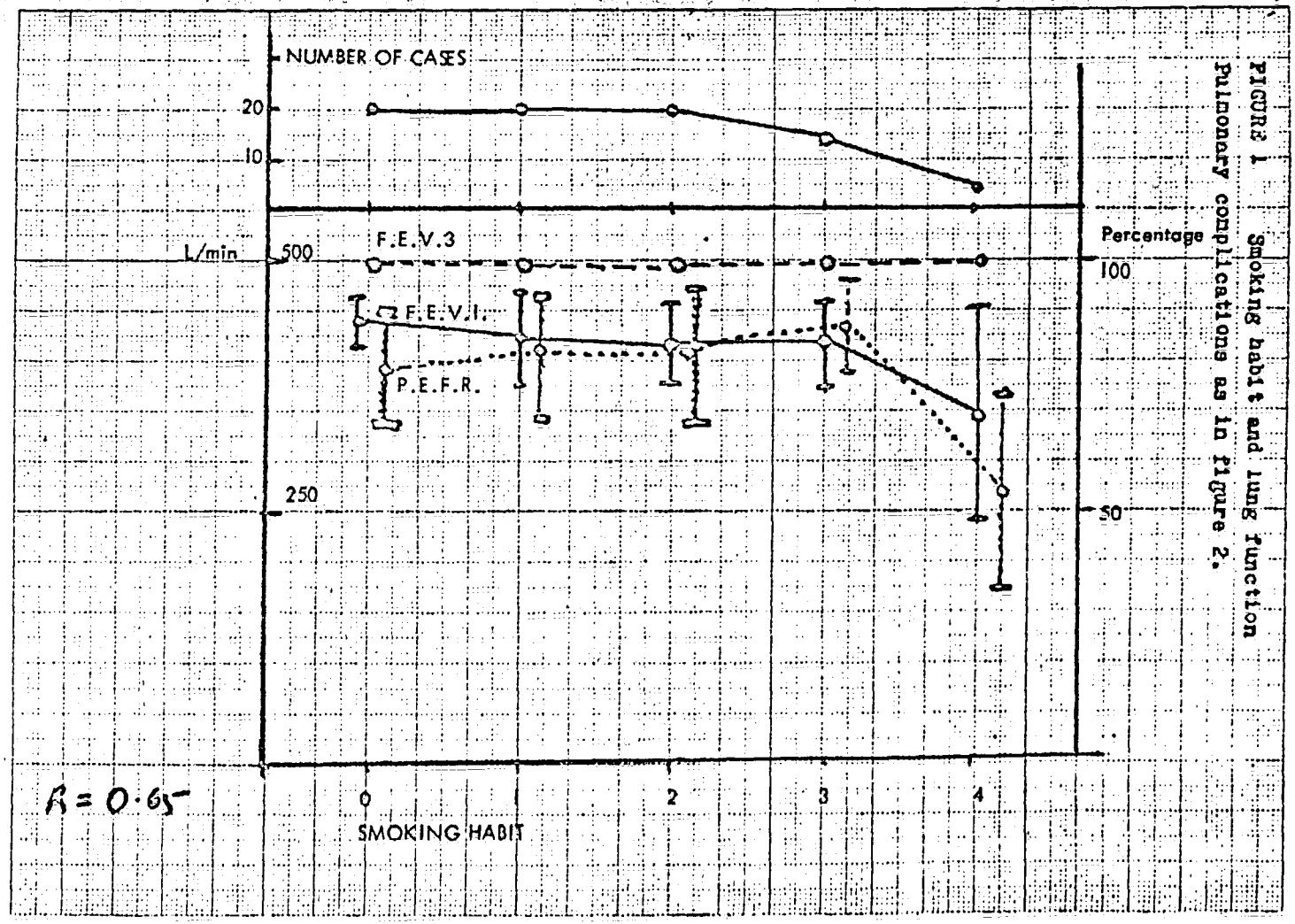

FIGURE 1 Smoking habit and lung function
Pulmonary complications as in figure 2.

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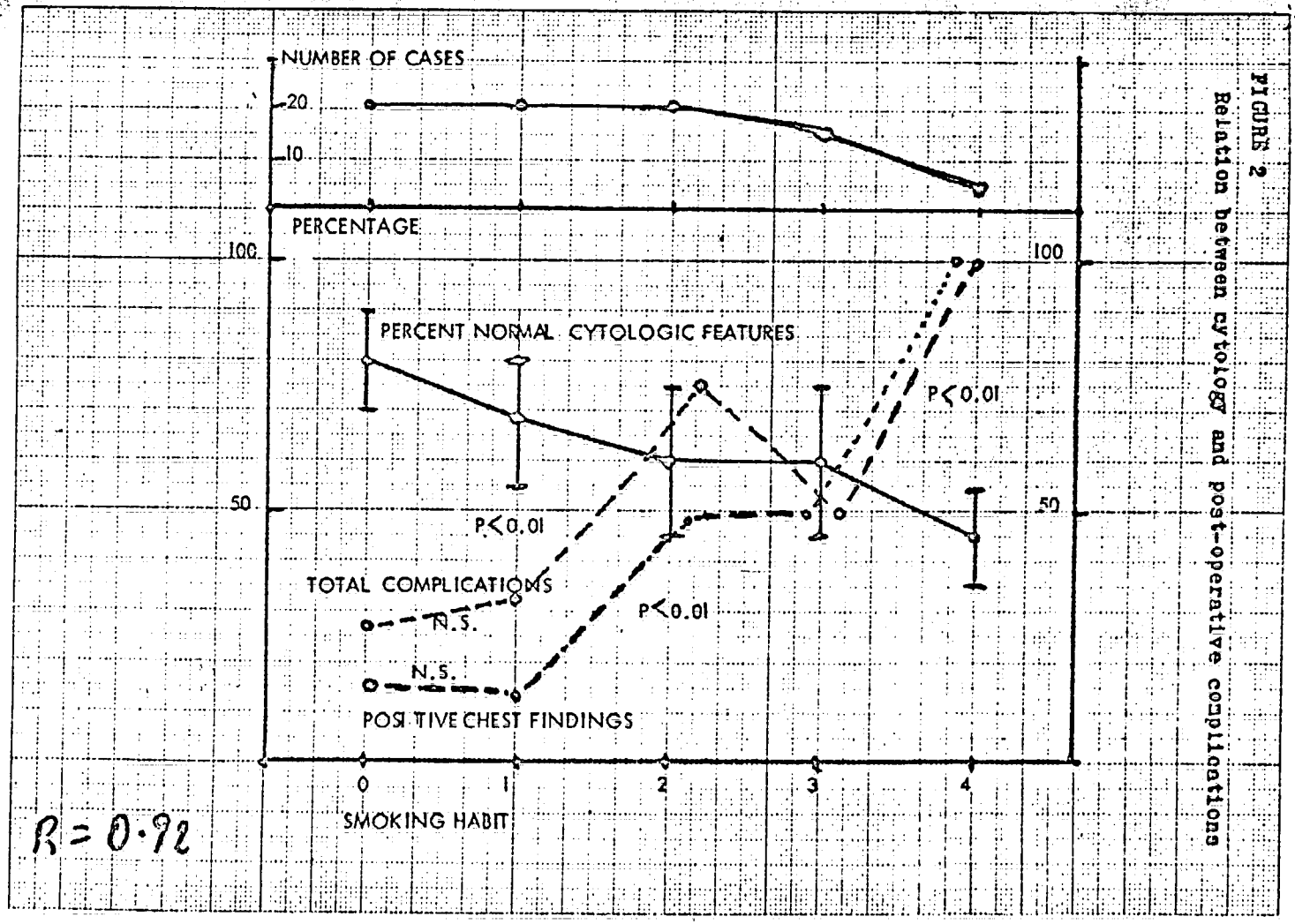

FIGURE 2
Relation between cytology and post-operative complications

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Type of Study	Smoking habit	Rate of decay of cytologic features during anesthesia		
		N	$\bar{X}$	SD
DRY GASES	Non smokers and light smokers	15	67	15
	Medium and heavy smokers	9	53	9
Gases with 60% Relative Humidity	Non smokers and light smokers	10	85	11
	Medium and heavy smokers	7	85	11

TABLE I.

Effects of smoking habit on rate of decay of cytologic features during anesthesia in patients breathing dry and 60% humidified gases

Non smokers and light smokers: 0-9 cigarettes a day
Medium and heavy smokers : 10 or more cigarettes a day

N: number of cases, $\bar{X}$: Mean measurement SD: standard deviation from the mean.

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